Pressurised IntraPeritoneal Aerosolised Chemotherapy in the management of cancers of the colon, ovary and stomach: a randomised controlled phase II trial of efficacy in peritoneal metastases (PICCOS)

Trial Synopsis

Chief Investigators	Professor Jared Torkington Mrs Sadie Jones *(both of Cardiff and Vale University Health Board)*	
Lead Investigators	Colorectal group	Oncology Lead: Professor Richard Adams *(Cardiff University)*
		Surgical Lead: Professor Jamie Murphy *(Imperial College London)*
	Ovarian group	Oncology Lead: Dr Emma Hudson *(Velindre NHS Trust)*
		Surgical Lead: Mr Jonathon Frost *(Royal United Hospital Bath NHS FT)*
	Stomach group	Oncology Lead: Dr Sarah Gwynne *(Swansea Bay UHB)*
		Surgical Lead: Mr Christopher Peters *(Imperial College London)*
	Lead Radiologist	Professor Gina Brown *(Imperial College London)*
	Health Related QoL	Professor Deborah Fitzsimmons *(Swansea University)*
	Qualitative Interview Sub study	Professor Jane Blazeby *(University of Bristol)*
Sponsor	Cardiff and Vale University Health Board	
Coordinating Trials Unit	Centre for Trials Research, Cardiff University	
Funder	NIHR	
Trial design	Phase II, multicentre, unblinded, basket trial, randomised controlled trial	
Trial participants	Patients with colorectal, ovarian or stomach cancer with peritoneal metastases (PM)	
Planned sample size	Colorectal group: 78	
	Ovarian group: 66	
	Stomach group: 72	
Planned number of sites	30 Recruiting sites *(Type A sites)* 10 Recruiting and PIPAC sites *(Type B sites). All sites based in the UK*	
Site types in the trial	Type A sites - Recruiting site activities: • Participant consent, screening and randomisation • Administer systemic anti-cancer therapy (SACT) to participants in both arms (as per disease group in protocol) • Participant follow up • Pharmacovigilance	Type B sites – Recruiting and PIPAC site activities: • Same activities as A plus perform PIPAC on participants in intervention arm both for those recruited at own site and those referred from type A sites

	• Pre-op assessments for PIPAC procedures	
Planned trial period	• Trial set up: 6 months (Nov 2022 – April 2023) • Recruitment period: 2.5 years (May 2023 – October 2026) • Follow up period: at least 6 months from randomisation (Sept 2023 – April 2026) • Analysis and report writing: 6 months (May2026 – October 2026) • 4 years total	
Trial email	PICCOS@cardiff.ac.uk	

Trial Objectives

Primary objective:

- To determine if PIPAC given with (colorectal, stomach) or instead of (ovarian) systemic anti-cancer therapy (SACT) improves Peritoneal Progression Free Survival (pPFS) compared to standard SACT

Secondary objectives:

- To determine how PIPAC impacts quality of life (QoL) compared to standard of care (SOC).
- To determine the safety of PIPAC in terms of the proportion of patients experiencing toxicity and/or surgical complications, compared with SACT only group.
- To determine the proportion of patients who complete three PIPAC procedures.
- To determine if disease can be reduced to the point of resectability.
- To evaluate Overall Survival (OS) in both groups.
- To evaluate overall Progression Free Survival (PFS) in both groups.
- To assess the impact on patient's symptoms (and need for intervention to relieve them – in ovarian cancer).
- To determine peritoneal specific overall response rate (ORR) and disease control rate (DCR).

Tertiary/exploratory objectives

- To determine the feasibility of randomisation.
- Explore stakeholder perspectives and experiences of PIPAC treatment, including its impact on symptoms and QoL.
- To determine the patient related outcomes of interest for patients with PM undergoing PIPAC and establish if a new measurement scale/item is needed.
- To identify/develop a patient reported measure for patients with PM undergoing PIPAC and test this in patients recruited in the latter half of the trial.
- To evaluate and compare between the two arms the response of Carcinoembryonic Antigen (CEA) (in colorectal cancer) and Cancer Antigen 125 (CA125) (in ovarian cancer) with the radiological response of peritoneal disease.
- To cross correlate the radiological evaluation to assess scan effectiveness and mismatches with PCI scoring at laparoscopy.

Trial Outcome Measures

Primary outcome:

- Peritoneal Progression Free Survival (pPFS)

Secondary outcomes:

- QoL (EORTC QLQ C30)
- Safety and surgical complication rates
    - Toxicity and grade according to NCI Common Terminology Criteria for Adverse Events (CTCAE) V5.0
        - Episodes of neutropenic sepsis
    - Clavien Dindo classification (within 30 days of each PIPAC)
    - Incidence of radiologically proven bowel obstruction
- Proportion of patients completing 3 PIPAC procedures, and reasons why not if <3 completed.
- Number of conversions to operable disease in stomach or colorectal cancer
- OS, defined as days from randomisation to death for any reason.
- PFS. This is defined as the time from date of randomisation to the date of progression (anywhere in the patient) or death from any cause.
    - Extraperitoneal Progression free survival (ePFS), defined as the time from date of randomisation to the date of progression (outside of the peritoneum) or death from any cause.
- Episodes of therapeutic ascitic drainages (in ovarian cancer)
- Peritoneal specific ORR observed at any time during treatment and follow-up.
- Peritoneal specific DCR defined as the proportion of patients with complete response, partial response or stable disease maintained at end of treatment scan (i.e. 3rd scan).

Tertiary/exploratory outcomes:

- The proportion of eligible patients who consent to randomisation out of those invited to take part.
- Patient related outcomes of interest in patients with PM undergoing PIPAC as determined by qualitative interviews with healthcare professionals and patients.
- Identification/development of a patient-reported measure for patients with PM undergoing PIPAC.
- CEA (in colorectal cancer) and CA125 (in ovarian cancer) response from baseline to the end of follow up.
- PCI scoring at laparoscopy.

Eligibility Criteria

Inclusion Criteria

All disease groups:

- 16 Years and older
- Visible (measurable or non-measurable) peritoneal lesion(s) on computerised tomography (CT) imaging as per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1
- Eastern Cooperative Oncology Group (ECOG) performance status 0–1
- Adequate bone marrow, liver and kidney function, and coagulation parameters (within 7 days prior to randomisation):
    a) Neutrophil ≥ 1.5×109/L
    b) White blood cells ≥ 3.0 x 109/L
    c) Platelets ≥ 100×109/L

d) Haemoglobin ≥ 90 g/l
e) Serum bilirubin ≤3 x ULN
f) ALT/AST ≤ 2.5 x ULN
g) Creatinine clearance ≥60 mls/min

- Fit enough to receive full dose of SACT in cycle 1 as defined in the protocol.
- Ability to provide informed consent obtained prior to any trial-specific screening procedures.

Colorectal group only:
- Peritoneal Metastasis (PM) from histologically proven primary adenocarcinoma of the colorectum.

Ovarian group only:
- PM from histologically confirmed primary epithelial ovarian, tubal, or primary peritoneal platinum-resistant carcinoma (including clinical recurrence, refractory disease, or persistent disease within 6 months of last chemotherapy).

Stomach group only:
- PM from histologically proven primary adenocarcinoma (any subtype) of stomach or Siewert type 3 gastro-oesophageal junction tumour.
- Any Human Epidermal Growth Factor Receptor 2 (HER2) status or Combined Positive Score (CPS).

Exclusion criteria
All disease groups:
- Any prior malignancy not considered in complete remission for at least 2 years, excluding non-melanoma skin cancer
- Pregnant or breastfeeding
- Untreated central nervous system disease or symptomatic central nervous system metastasis, history or evidence of thrombotic or haemorrhagic disorders not considered currently in complete remission
- Bevacizumab / Aflibercept should not be used in either arm (minimum 4 weeks from any prior bevacizumab / Aflibercept)
- Contraindication to any drug contained in the chemotherapy regimen
- Medical, geographical, sociological, psychological, or legal conditions that would prevent the patient from completing the study or signing the informed consent
- Unresolved bowel obstruction or parenteral nutrition or gastric tube
- Contraindication to surgery
- Participating in other oncological trials that may impact on endpoint

Colorectal group only:
- Extra-peritoneal metastases except for:
  a) retroperitoneal lymph nodes <2cm,
  b) lung metastases; with < 5 lung metastases none >1cm
- Eligible for and choses cytoreductive surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) upfront
- Prior systemic therapy for colorectal cancer in the last 6 months
- Dihydropyrimidine Dehydrogenase Deficiency (DPYD) variant detected
- Microsatellite instability (MSI) high

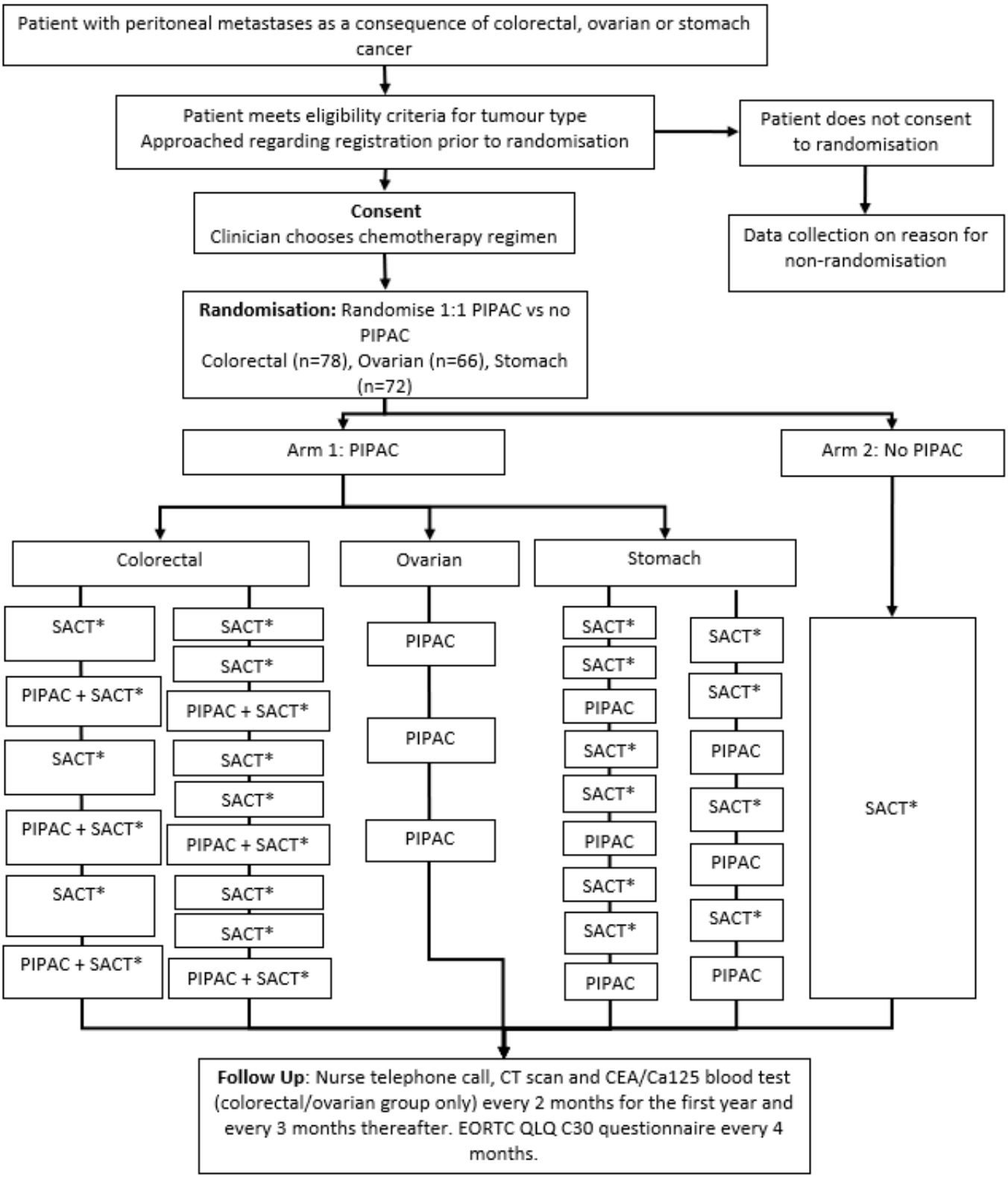
Ovarian group only:

- Extra-peritoneal metastases (with the exception of retroperitoneal lymph nodes)
- Parenchymal liver or spleen metastases
- Malignant pleural effusion
- Non-epithelial pathology subtype
- Peritoneal disease, amenable to surgical resection
- Radiological suspicion of involved lymph nodes (e.g. radiological features suspicious of malignancy)

Stomach group only:

- Extra-peritoneal metastases (with the exception of retroperitoneal lymph nodes)
- Prior systemic anti-cancer therapy, radiotherapy or surgery for stomach cancer
- Gastric or duodenal stent in-situ
- Gastro-oesophageal junction Sievert Type 1 or Type 2 tumour
- Symptoms and/or radiology suggestive of impending and/or current bowel obstruction
- Uncontrolled and persistent ascites
- MSI high
- DPYD variant detected

Trial Schema



* SACT = Systemic Anti-Cancer Therapy. Should be as per standard of care options listed within the PICCOS protocol. There are 2 or 3 weekly options for colorectal/ stomach groups, regimen given is chosen by treating clinician, ovarian SACT is 4 weekly.

Trial Treatment

Prior to randomisation, the treating Investigator will select the SACT regimen most appropriate to the individual patient from the options available in the protocol for the patient's disease group.
Following randomisation, treatment should commence within 2 weeks for all participants other than those in the ovarian intervention arm, for whom first PIPAC should take place within 3 weeks.

There is no trial specific drug provision, all drugs used in the trial will be taken from local hospital supplies.

IMPs:

- Colorectal group: Oxaliplatin IP via PIPAC, Mitomycin IP via PIPAC
- Ovarian group: Cisplatin IP via PIPAC, Doxorubicin IP via PIPAC, Paclitaxel IV, Liposomal doxorubicin IV, Gemcitabine IV
- Stomach group: Cisplatin IP via PIPAC, Doxorubicin IP via PIPAC

Treatment duration:

- Colorectal group: Intervention arm = 18 weeks, Control arm = 18 weeks
- Ovarian group: Intervention arm = 14 or 15 weeks, Control arm = 18 or 24 weeks
- Stomach group: Intervention arm = 18 or 21 weeks, Control arm = 18 weeks

Figure 1 Colorectal group treatment schema

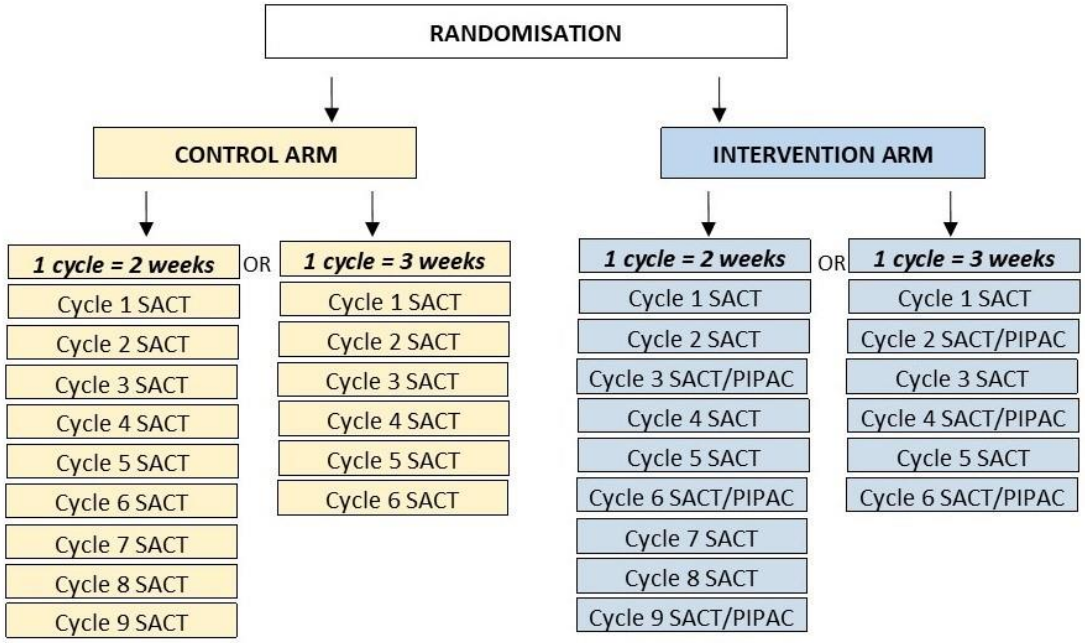


Table 1 Colorectal group dosing schedule

	Control arm- Colorectal	**Intervention arm- Colorectal**	
Option No. Cycle length	**SACT control arm**	**SACT**	**PIPAC chemotherapy**
Option 1 = FOLFOX	On day 1 of each cycle: *(9 cycles total)* • Oxaliplatin 85mg/m2 IV	On day 1 of cycles where PIPAC is not given: FOLFOX	Cycles 3, 6 and 9: • Oxaliplatin 92mg/m^2 IP OR

	Control arm- Colorectal	Intervention arm- Colorectal	
Option No. Cycle length	**SACT control arm**	**SACT**	**PIPAC chemotherapy**
2 weekly cycles	• Fluorouracil (5FU) 400mg/m2 IV bolus, infusion over 2 to 6 hrs • 5FU 2400mg/m^2 continuous IV, infusion over 46hrs • Sodium Folinate 350mg IV infusion infused over 1 to 2 hours OR calcium folinate 300 or 350mg IV infusion over 2 hours	• Oxaliplatin 85mg/m^2 IV • 5FU 400mg/m^2 IV bolus infuse over 2-6 hours • 5FU 2400mg/m^2 continuous IV infusion over 46hrs • Sodium Folinate 350mg IV infusion OR calcium folinate 300 or 350mg IV infusion On cycles 3, 6, 9 where PIPAC is <u>also</u> given: • 5FU 2400mg46hrs /m^2 continuous IV infusion over should be administered with pump disconnection 24 hours pre PIPAC or pump attachment 48 hours after PIPAC.	• Mitomycin C 7.5mg/m^2 IP *(if contraindication to Oxaliplatin)* *PIPAC should be scheduled day 3 to day 7 of the cycles to ensure a break of 24 hours between finishing the 5FU infusion and having PIPAC. If it is not possible to schedule the 5FU infusion prior to a participant's PIPAC it can be administered 48 hours or more after the PIPAC.* Subsequent non PIPAC cycles should occur a minimum of 10 days after completion of the 5FU infusion.
<u>Option 2 = FOLFOX + Cetuximab</u> 2 weekly cycles	Each cycle: *(9 cycles total)* • FOLFOX (as in option 1) plus on day of each 2 week cycle: (9 cycles total). • Cetuximab 500mg/m^2 IV (initial dose over 2 hrs, subsequent doses over 1 hour)	On day 1 of cycles where PIPAC is <u>not</u> given: • FOLFOX (as in option 1) • Cetuximab 500mg/m^2 IV (initial dose over 2 hrs, subsequent doses over 1 hour) On cycles 3, 6, 9 where PIPAC is <u>also</u> given: • 5FU infusion 2400mg/m^2 continuous IV infusion over 46hrs should be administered with pump disconnection 24 hours pre PIPAC or pump attachment 48 hours after PIPAC • Cetuximab 500mg/m^2 IV infusion over 1 hour	Cycles 3, 6 and 9 Oxaliplatin or Mitomycin as in option 1.
<u>Option 3 = FOLFOX + Panitumumab</u> 2 weekly cycles	Each cycle: *(9 cycles total)* • FOLFOX (as in option 1) • Panitumumab 6mg/Kg IV (initial dose over 1 hour,	On day 1 of cycles where PIPAC is <u>not</u> given: • FOLFOX (as in option 1) • Panitumumab 6mg/Kg IV (initial dose over 1	Cycles 3, 6 and 9: Oxaliplatin or Mitomycin as in option 1.

	Control arm- Colorectal	Intervention arm- Colorectal	
Option No. Cycle length	**SACT control arm**	**SACT**	**PIPAC chemotherapy**
	subsequent doses over 30 to 60 minutes)	hour, subsequent doses over 30 to 60 minutes) On cycles 3, 6, 9 where PIPAC is <u>also</u> given: • 5FU infusion 2400mg/m^2 continuous infusion over 46 hours • Panitumumab 6mg/Kg IV infused over 30 to 60 minutes	
<u>Option 4 =</u> **<u>FOLFIRI</u>** 2 weekly cycles	On day 1 of each 2 week cycle: *(9 cycles total)* • Irinotecan 180mg/m^2 IV infusion over 30 to 90 minutes • 5FU 400mg/m^2 IV bolus (can be given as infusion over 30 to 60 minutes) • 5FU 2400mg/m^2 continuous IV infusion over 46hrs • Sodium Folinate 350mg IV infusion over 1 to 2 hours OR calcium folinate 300 or 350mg IV infusion over 2 hours	On day 1 of cycles where PIPAC is <u>not</u> given: FOLFIRI • Irinotecan 180mg/m^2 IV infusion over 30 to 90 minutes • 5FU 400mg/m^2 IV bolus (can be given as infusion over 30 to 60 minutes) • 5FU 2400mg/m^2 continuous IV infusion over 46hrs • Sodium Folinate 350mg IV infusion over 1 to 2 hours OR calcium folinate 300 or 350mg IV infusion over 2 hours On cycles 3, 6, 9 where PIPAC is <u>also</u> given: • 5FU infusion 2400mg/m^2 continuous IV infusion over 46hrs should be administered with pump disconnection 24 hours pre PIPAC or pump attachment 48 hours after PIPAC	Cycles 3, 6 and 9: Oxaliplatin or Mitomycin as in option 1.
<u>Option 5</u> <u>=</u> **<u>FOLFIRI +</u>** **<u>Cetuximab</u>** 2 weekly cycles	Each cycle: *(9 cycles total)* • FOLFIRI (as in option 4) <u>plus</u> • Cetuximab 500mg/m^2 IV (initial dose over 2 hours,	On day 1 of cycles where PIPAC is <u>not</u> given: • FOLFIRI (as in option 4) • Cetuximab IV 500mg/m^2 IV (initial dose over 2 hours,	Cycles 3, 6 and 9: Oxaliplatin or Mitomycin as in option 1.

	Control arm- Colorectal	Intervention arm- Colorectal	
Option No. Cycle length	**SACT control arm**	**SACT**	**PIPAC chemotherapy**
	subsequent doses over 1 hour)	subsequent doses over 1 hour) On cycles 3, 6, 9 where PIPAC is <u>also</u> given: • 5FU 2400mg/m^2 continuous IV infusion over 46hrs should be administered with pump disconnection 24 hours pre PIPAC or pump attachment 48 hours after PIPAC • Cetuximab IV 500mg/m^2 IV infusion over 1 hour	
<u>Option 6 = FOLFIRI + Panitumumab</u> 2 weekly cycles	Each cycle: *(9 cycles total)* • FOLFIRI (as in option 4) <u>plus</u> • Panitumumab 6mg/Kg IV (initial doses over 1 hour, subsequent doses over 30-60 minutes)	On day 1 of cycles where PIPAC is not given: • FOLFIRI (as in option 4) • Panitumumab 6mg/Kg IV (initial doses over 1 hour, subsequent doses over 30-60 minutes) On cycles 3, 6, 9 where PIPAC is <u>also</u> given: • 5FU infusion 2400mg/m^2 continuous infusion over 46hrs should be administered with pump disconnection 24 hours pre PIPAC or pump attachment 48 hours after PIPAC • Panitumumab 6mg/Kg IV infused over 30-60 minutes	Cycles 3, 6 and 9: Oxaliplatin or Mitomycin as in option 1.
<u>Option 7 = CAPOX</u> 3 weekly cycles	Each 3 week cycle: *(6 cycles total)* • Oxaliplatin 130mg/m^2 IV infused over 2-6 hours • Capecitabine 1000mg/m^2 bd for 14 days (days 1-14 of the cycle) PO	On cycles where PIPAC is <u>not</u> given: • Oxaliplatin 130mg/m^2 IV infused over 2 to 6 hrs on day 1 • Capecitabine 1000mg/m^2 bd for 14 days (days 1-14 of the cycle) PO	Cycles 2, 4 and 6: • Oxaliplatin 92mg/m^2 IP OR • Mitomycin C 7.5mg/m^2 IP *(if contraindication to Oxaliplatin* Subsequent non PIPAC cycles should occur a minimum of 6 days

	Control arm- Colorectal	Intervention arm- Colorectal	
Option No. Cycle length	**SACT control arm**	**SACT**	**PIPAC chemotherapy**
		On cycles where PIPAC is given: • Capecitabine 1000mg/m^2 bd for 14 days (days 1-14 of the cycle) PO. *Capecitabine should be omitted for 24 hours prior to the PIPAC procedure and for 48 hours afterwards. Missed tablets should not be replaced (thus only 11 days of tablets are required)*	after completion of the last capecitabine tablets
In all cases dose reductions from prior cycles will be maintained			

Notes for colorectal group:

- Participants who show extraperitoneal progression and have not yet completed the treatment period may switch to an alternative SACT regime listed in the protocol at the discretion of their treating PI.

Figure 2 Ovarian group treatment schema

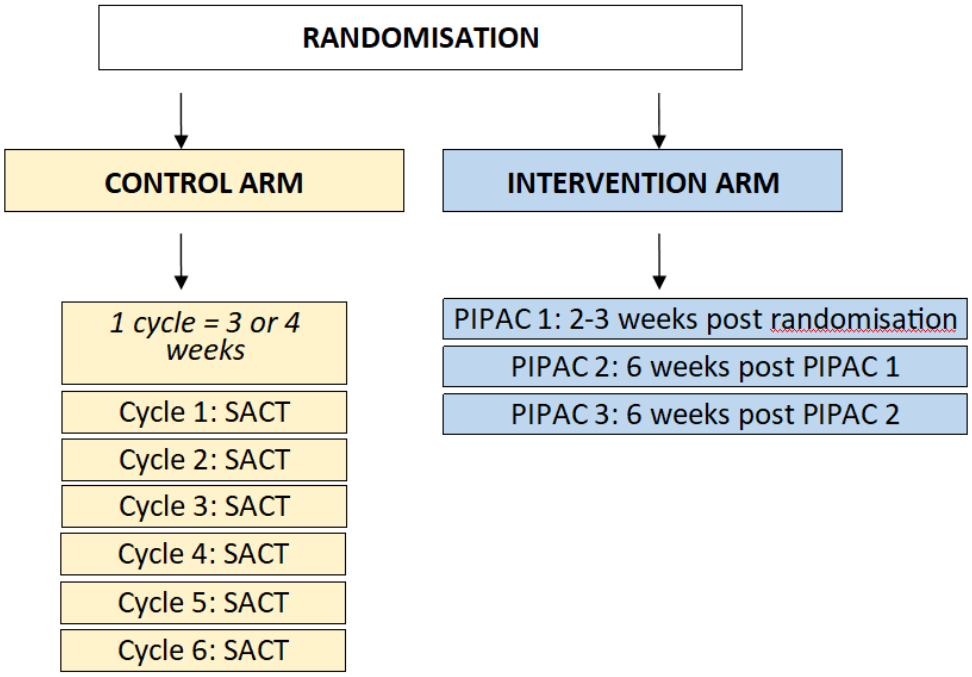


Table 2 Ovarian group dosing schedule

	Control arm - Ovarian	**Intervention arm- Ovarian**	
Option No Cycle length	**SACT**	**SACT**	**PIPAC**
Option 1 *4 weekly cycles*	On days 1, 8, 15 of each 4 week cycle: (6 cycles total) • Paclitaxel 80mg/m^2 IV infusion over 3 hrs	None	PIPAC 1: 2-3 weeks after randomisation PIPAC 2: PIPAC 1 + 6 weeks PIPAC 3: PIPAC 2 + 6 weeks • Cisplatin 10.5mg/m^2 IP • Doxorubicin 2.1mg/m^2 IP
Option 2 *4 weekly cycles*	On day 1 of each 4 week cycle: (6 cycles total) • Liposomal doxorubicin 50mg/m^2 IV infusion. Initial dose at 1mg/minute (so 100mg dose over 100 minutes), subsequent doses over 60 minutes.	None	As in option 1
Option 3 *3 weekly cycles*	On days 1, 8 and 15 of each 3 week cycle: (6 cycles total) • Gemcitabine 1000mg/m^2 IV infusion	None	As in option 1

Notes for ovarian group:

- Participants who show extraperitoneal progression and have not yet completed the treatment period may switch to an alternative SACT regime in the control arm or have SACT added in, in the intervention arm, at the discretion of their treating PI. If chemotherapy is added to intervention arm, it should be completed 7 days prior to the PIPAC procedure.

Figure 3 Stomach group treatment schema

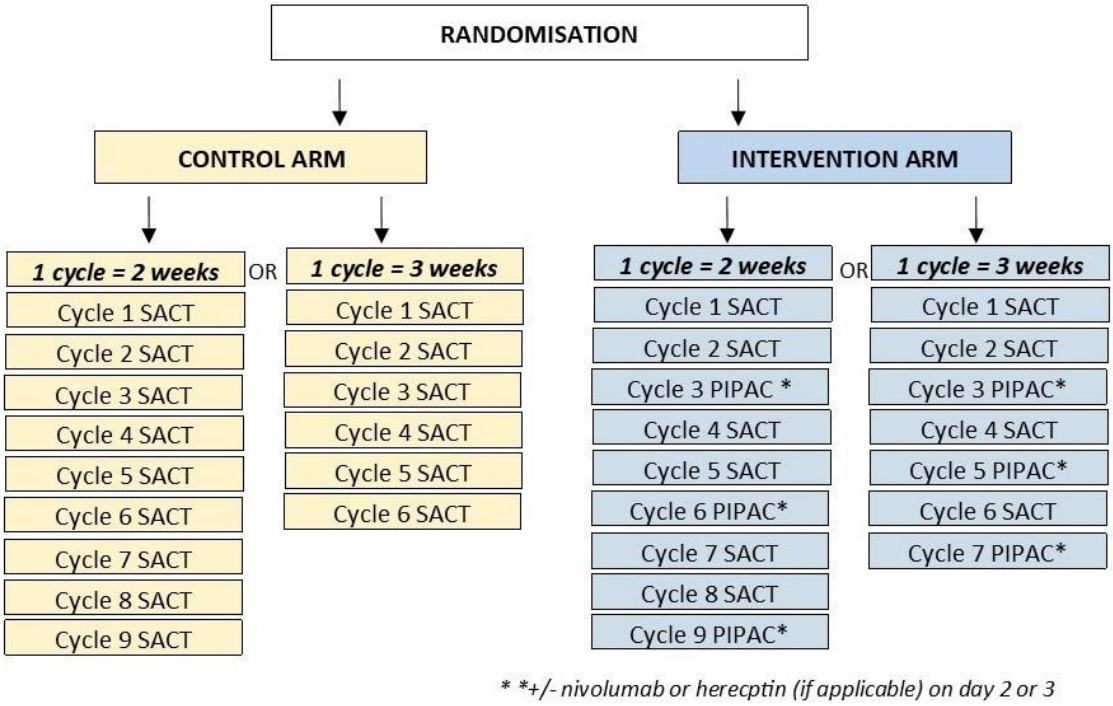


Table 3 Stomach group dosing schedule

	Control arm- Stomach	**Intervention arm- Stomach**		
Option No, *Cycle length*	**Systemic chemotherapy**	**Systemic chemotherapy**	**PIPAC chemotherapy**	**Comments**
HER 2 negative patients:				
Option 1 = FOLFOX- 2 weekly cycles	On day 1 of each 2 week cycle: *(9 cycles total)* • Oxaliplatin 85mg/m² infused IV over 2 to 6 hrs • 5FU bolus 400mg/m² given as IV infusion over 30 to 60 minutes • 5FU infusion 2400mg/m² IV continuous infusion over 46hrs • Sodium Folinate 350mg IV OR calcium folinate 300 or 350mg IV infusion over 1 to 2 hours	On day 1 of each 2 week cycle: *(6 cycles total)* • Oxaliplatin 85mg/m² infused IV over 2 to 6 hrs • 5FU bolus 400mg/m² given as IV infusion over 30 to 60 minutes • 5FU infusion 2400mg/m² IV continuous infusion over 46hrs • Sodium Folinate 350mg IV OR calcium folinate 300 or 350mg IV infusion over 1 to 2 hours *IV SACT is OMITTED during PIPAC cycles (i.e. cycle 3, 6 and 9)*	Cycles 3, 6 and 9 during PIPAC procedure: • Cisplatin 10.5mg/m² IP • Doxorubicin 2.1mg/m² IP	

	Control arm- Stomach	Intervention arm- Stomach		
Option No, *Cycle length*	**Systemic chemotherapy**	**Systemic chemotherapy**	**PIPAC chemotherapy**	**Comments**
Option 2 = CAPOX- 3 weekly cycles	Each 3 week cycle: *(6 cycles total)* • Oxaliplatin 130mg/m² via IV infused over 2 to 6 hrs • Capecitabine 1000mg/m² bd (PO Days 1-14)	Each 3 week cycle: *(4 cycles total)* • Oxaliplatin 130mg/m² via IV infused over 2 to 6 hrs • Capecitabine 1000mg/m² bd (PO Days 1-14) *IV SACT is OMITTED during PIPAC cycles (i.e. cycle 3,5 and 7)*	Cycles 3, 5 and 7 during PIPAC procedure: • Cisplatin 10.5mg/m² IP • Doxorubicin 2.1mg/m² IP	Please note a 14 day capecitabine regime (not 21 days) is required to allow a 7 day chemotherapy washout prior to PIPAC
Option 3 = CX- 3 weekly cycles	Each 3 week cycle: *(6 cycles total)* • Cisplatin 60mg/m² IV day 1 • Capecitabine 1000mg/m² bd (PO Days 1-14)	Each 3 week cycle: *(4 cycles total)* • Cisplatin 60mg/m² IV day 1 • Capecitabine 1000mg/m² bd (PO Days 1-14) *IV SACT is OMITTED during PIPAC cycles (i.e. cycle 3, 5 and 7)*	Cycles 3, 5 and 7 during PIPAC procedure: • Cisplatin 10.5mg/m² IP • Doxorubicin 2.1mg/m² IP	Please note a 14 day capecitabine regime (not 21 days) is required to allow a 7 day chemotherapy washout prior to PIPAC
HER 2 positive patients:				
Option 4 = CXtraz 3 weekly cycles Trastuzumab to be used as per current NICE recommendation.	Each 3 week cycle: *(6 cycles total)* • CX as per option 3 • Trastuzumab* IV Cycle 1 8mg/kg over 90 minutes. Subsequent cycles 6mg/kg over 30 minutes	On day 1 of each 3 week cycle: *(4 cycles total)* • CX as per option 3 • Trastuzumab* IV Cycle 1 8mg/kg over 90 minutes. Subsequent cycles 6mg/kg over 30 minutes *IV Chemotherapy is OMITTED during PIPAC cycles (i.e. cycle 3, 5 and 7)* **However trastuzumab should be continued throughout PIPAC cycles, given D3 post PIPAC**	Cycles 3, 5 and 7 during PIPAC procedure: • Cisplatin 10.5mg/m2 IP • Doxorubicin 2.1mg/m² IP	Please note a 14 day capecitabine regime (not 21 days) is required to allow a 7 day chemotherapy washout prior to PIPAC *Trastuzumab should be continued 3 weekly throughout PIPAC. Maintenance trastuzumab may be continued upon completion of planned trial treatment (if clinically indicated)
Option 5 = CAPOX + Trastuzumab- 3 weekly cycles	Each 3 week cycle: *(6 cycles total)* • CAPOX as in option 2 • Trastuzumab* IV Cycle 1 8mg/kg over	Each 3 week cycle: *(4 cycles total)* • CAPOX as in option 2 • Trastuzumab* IV Cycle 1 8mg/kg over 90	Cycles 3, 5 and 7 during PIPAC procedure: • Cisplatin 10.5mg/m² IP	Please note a 14 day capecitabine regime (not 21 days) is required to allow a 7 day chemotherapy

	Control arm- Stomach	Intervention arm- Stomach		
Option No, *Cycle length*	**Systemic chemotherapy**	**Systemic chemotherapy**	**PIPAC chemotherapy**	**Comments**
Trastuzumab to be used as per current NICE recommendation.	90 minutes, subsequent cycles 6mg/kg over 30 minutes	minutes, subsequent cycles 6mg/kg over 30 minutes IV and oral Chemotherapy is OMITTED during PIPAC cycles (i.e. cycle 3, 5 and 7) **However trastuzumab should be continued throughout PIPAC cycles, given D3 post PIPAC**	• Doxorubicin 2.1mg/m^2 IP	washout prior to PIPAC *Trastuzumab should be continued 3 weekly throughout PIPAC. Maintenance trastuzumab may be continued upon completion of planned trial treatment (if clinically indicated)
<u>Option 6 = FOLFOX + Trastuzumab</u> 2 weekly cycles Trastuzumab to be used as per current NICE recommendation.	On day 1 of each 2 week cycle: *(9 cycles total)* • FOLFOX as per option 1 PLUS 3 weekly • Trastuzumab* IV Cycle 1 8mg/kg over 90 minutes, subsequent cycles 6mg/kg over 30 minutes	On day 1 of each 2 week cycle: *(6 cycles total)* • FOLFOX as per option 1 PLUS 3 weekly • Trastuzumab* IV Cycle 1 8mg/kg over 90 minutes, subsequent cycles 6mg/kg over 30 minutes IV chemotherapy is OMITTED during PIPAC cycles (i.e. cycle 3, 6 and 9) **However trastuzumab should be continued throughout PIPAC cycles, given D3 post PIPAC**	Cycles 3, 6 and 9 during PIPAC procedure: • Cisplatin 10.5mg/m^2 IP • Doxorubicin 2.1mg/m^2 IP	*Trastuzumab should be continued 3 weekly throughout PIPAC. Maintenance trastuzumab may be continued upon completion of planned trial treatment (if clinically indicated)
<u>Patients eligible for immunotherapy in line with current NICE recommendations (currently HER –2 negative, CPS ≥5)</u>				

	Control arm- Stomach	Intervention arm- Stomach		
Option No, *Cycle length*	**Systemic chemotherapy**	**Systemic chemotherapy**	**PIPAC chemotherapy**	**Comments**
Option 7 = CAPOX + Nivolumab 3 weekly cycles Nivolumab to be used as per current NICE recommendation.	Each 3 week cycle: *(6 cycles total)* • CAPOX as per option 2 • Nivolumab** 360mg IV over 30 minutes day 1	Each 3 week cycle: *(4 cycles total)* • CAPOX as per option 2 • Nivolumab ** 360mg IV day 1 IV and oral Chemotherapy is OMITTED during PIPAC cycles (i.e. cycle 3, 5 and 7) **However nivolumab should be continued throughout PIPAC cycles, given D3 post PIPAC**	Cycles 3, 5 and 7 during PIPAC procedure: • Cisplatin 10.5mg/m^2 IP • Doxorubicin 2.1mg/m^2 IP	Please note a 14 day capecitabine regime (not 21 days) is required to allow a 7 day chemotherapy washout prior to PIPAC **Nivolumab should be continued 3 weekly throughout PIPAC cycles. Maintenance nivolumab may be continued upon completion of planned trial treatment (if clinically indicated)
Option 8 = FOLFOX + Nivolumab 2 weekly cycles Nivolumab to be used as per current NICE recommendation.	On day 1 of each 2 week cycle: *(9 cycles total)* • FOLFOX as per option 1 • Nivolumab** 240mg IV over 30 minutes day 1	On day 1 of each 2 week cycle: *(7 cycles total)* • FOLFOX as per option 1 • Nivolumab** 240mg IV day 1 IV chemotherapy is OMITTED during PIPAC cycles (i.e. cycle 4, 7 and 10) **However Nivolumab should be continued throughout PIPAC cycles, given D3 post PIPAC**	Cycles 3, 6 and 9 during PIPAC procedure: • Cisplatin 10.5mg/m^2 IP • Doxorubicin 2.1mg/m^2 IP	Please note a 14 day capecitabine regime (not 21 days) is required to allow a 7 day chemotherapy washout prior to PIPAC **Nivolumab should be continued throughout PIPAC cycles. Maintenance nivolumab may be continued upon completion of planned trial treatment (if clinically indicated)

Note for stomach group:

- HER-2 directed therapy and immunotherapy allowed within their respective NICE recommendations
- IV cytotoxic chemotherapy is omitted during PIPAC cycles in the intervention arm
- If using 3 weekly capecitabine containing regimens, must use 14 days of capecitabine to allow washout period of 1 week before PIPAC
- Trastuzumab/ Nivolumab (if applicable) should be continued during PIPAC cycles to maintain standard schedule (day 3 post PIPAC)

- If trastuzumab is delayed, please follow appropriate re-loading guidance
- In the event that PIPAC does not go ahead on day 1 as planned, a +7 day window is allowed for PIPAC to be given before the next SACT needs to be deferred. If nivolumab or Herceptin are given on day 3 of a deferred PIPAC cycle the site is encouraged to give the nivolumab or herceptin as close as possible to the date next due (2 weeks later for 2 weekly nivolumab and 3 weeks later for 3 weekly nivolumab and Herceptin), recognising that this will lead to a disconnection between the cytotoxic SACT and the biological agent
- Herceptin/Nivolumab maintenance should continue after completion of trial schema (if clinically indicated) as per standard of care
- Maintenance cytotoxic chemotherapy post-completion of trial schema is not permitted in the gastric arm of the trial
- Participants who show extraperitoneal progression and have not yet completed the treatment period may switch to an alternative SACT regime listed in the protocol at the discretion of their treating PI.

Assessments

Screening assessments

Table 4 Screening assessments

Screening test	Timescale
Medical history and physical examination	Within 28 days prior to randomisation
Performance status assessment (ECOG)	Within 28 days prior to randomisation
Urine pregnancy test (woman of childbearing potential (WOCBP) only)	Within 7 days prior to randomisation
Assessment of concomitant medications	Within 28 days prior to randomisation
CT scan with contrast (thorax, abdomen and pelvis)	Within 28 days prior to randomisation
Bloods (U&E, FBC, LFT, eGFR, coagulation screen, bone profile, DPYD testing*)	Within 7 days prior to randomisation except DPYD testing that can be performed any time prior to randomisation
MSI*, HER2** and CPS** testing on tumour biopsy	Any time prior to randomisation

** Applicable to colorectal and stomach groups only*
*** Applicable to stomach group only*

Baseline assessments

Table 5 Baseline assessments

Assessment	Timepoint
Assessment of tumour markers (CEA for colorectal / CA125 for ovarian group)	Within 4 weeks prior to day 1 of cycle 1
Ethnicity documentation	After trial consent but prior to first cycle of SACT or PIPAC
EORTC QLQ-C30 (quality of life questionnaire)	After trial consent but prior to first cycle of SACT or PIPAC

Assessments prior to each SACT cycle

Table 6 Assessments prior to each SACT cycle

Assessment	Timepoint

Physical exam (including height, weight)	Within 72 hours, or as per local practice
Vital signs (including blood pressure, heart rate)	Within 72 hours, or as per local practice
Bloods (including U&E, FBC, LFT, eGFR, bone profile)	Within 72 hours, or as per local practice
Adverse Events (AE)/ SAEs	During the PV reporting period
Concomitant medications	Within 72 hours, or as per local practice
ECOG performance status assessment	Within 72 hours, or as per local practice
Assessment of tumour marker (CA125 for ovarian patients, CEA for colorectal patients, not applicable to stomach patients)	Within 72 hours, or as per local practice

Assessments prior to each PIPAC cycle (pre-op assessments) – *these can take place at the 'Recruiting centre' or the 'Recruiting and PIPAC centre'*

Table 7 Assessments prior to each PIPAC cycle

Assessment	**Timepoint**
Physical assessment (including height, weight)	Within 72 hours prior to PIPAC
Vital signs (including blood pressure, heart rate)	Within 72 hours prior to PIPAC
Bloods (including U&E, FBC, LFT, eGFRs, bone profile)	Within 72 hours prior to PIPAC
ECG *(dependent on pre-op assessment requirement and at discretion of clinician / anaesthetist)*	Within 72 hours prior to PIPAC
AEs/ SAEs	Within 72 hours prior to PIPAC
Concomitant medications	Within 72 hours prior to PIPAC
Urine pregnancy test (WOCBP only)	Within 72 hours prior to PIPAC
ECOG performance status assessment	Within 72 hours prior to PIPAC
Assessment of tumour marker (CA125 for ovarian patients, CEA for colorectal patients, not applicable to stomach patients)	Prior to PIPAC 3 only
Conversation with PIPAC centre if patient has ascites re: suitability for PIPAC/ if requires tap prior to travel	Minimum of 3 days prior to PIPAC

30 days after each PIPAC procedure, the site Research Nurse (RN) will call participants and review their medical notes to obtain information to document if any surgical complications have happened in the 30 days since the procedure – Clavien Dindo classification will be recorded in the CRF.

Follow up Assessments

All participants will be followed up to the point of peritoneal disease progression as per RECIST (v1.1) or a minimum of six months post-randomisation whichever comes first. Ongoing assessments will end for all patients when the last patient randomised has completed six months of follow up from their randomisation date or for the timeframes specified below. After the end of treatment, participants will have a telephone call from the site RN every 2 months in the first year and then 3 monthly thereafter just prior to each CT scan to review progress and collect follow up data as per the table below.

Table 8 Assessments in follow up

Assessment	**Timepoint**
AEs/ SAEs	For up to 30 days post end of trial treatment only

Documentation of bowel obstruction since last trial visit/ phone call (admissions to hospital or the cause of prolonged hospitalisation – record on Toxicity CRF) – *RN from site to call participants to obtain this information prior to each CT scan in the follow up period.*	For the first year following the last CT scan during the treatment period then every 3 months thereafter or as per local SOC for CT scanning frequency until peritoneal disease progression as per RECIST (v1.1) or end of trial.
CT scan (chest, abdomen and pelvis)	Every 2 months (+/- 2 weeks) for the first year following the last CT scan during the treatment period then every 3 months thereafter or as per local SOC until peritoneal disease progression as per RECIST (v1.1) or end of trial.
Blood test - CA125 for ovarian patients, CEA for colorectal patients (N/A stomach group patients)	Same timepoints as for CT scans until peritoneal disease progression as per RECIST (v1.1) or end of trial.
QoL questionnaire (EORTC QLQ-30)	2 months after end of treatment, then 4 monthly thereafter (+/- 2 weeks) until death or end of trial.
Details of further treatment for colorectal / ovarian or stomach cancer (as applicable) – document type of treatment given and number of lines of each. *(Information collected by RN at phone call and upon review of medical notes).*	Every 2 months (+/- 2 weeks) in first year after EOT, 3 monthly thereafter until progressive disease as per RECIST (v1.1) or end of trial.
Concomitant Medications	For up to 30 days post end of trial treatment only (i.e. same period as AEs/ SAEs).

CT scans in the trial

Ct scans of the chest, abdomen and thorax should be performed with contrast within the following timepoints:

- Colorectal group
  - Baseline (should be within 6 weeks prior to randomisation, ideally within 4 weeks)
  - 8-10 weeks post-randomisation
  - 19-21 weeks post-randomisation
- Ovarian group
  - Baseline (should be within 6 weeks prior to randomisation, ideally within 4 weeks)
  - 10-12 weeks post-randomisation
  - 18-20 weeks post-randomisation
- Stomach group
  - Baseline (should be within 6 weeks prior to randomisation, ideally within 4 weeks)
  - 8-10 weeks post-randomisation
  - 19-21 weeks post randomisation (2 weekly group) or 20-22 weeks post randomisation (3 weekly group)

All groups: 4th and thereafter: every 2 months +/- 2 weeks for the first year after the end of trial treatment, thereafter every 3 months (or as per local SOC) until end of trial. Trial specific CT scans (with RECIST measurements reported on the CRFs) will stop at the time of peritoneal disease progression as per RECIST (V1.1).

Site staff will be required to upload pseudonymised copies of CT scans to the Cimar cloud platform for central radiology review of the primary endpoint. Training will be provided at SIV.

Quality of Life questionnaires

EORTC QLQ C30 should be completed at the following timepoints:

- Colorectal
  - Baseline (after consent, and prior to treatment starting)
  - 8-10 weeks post-randomisation
  - 19-21 weeks post-randomisation
- Ovarian
  - Baseline (after consent, and prior to treatment starting)
  - 10-12 weeks post-randomisation
  - 18-20 weeks post-randomisation
- Stomach
  - Baseline (after consent, and prior to treatment starting)
  - 8-10 weeks post-randomisation
  - 19-21 weeks post randomisation (2 weekly group) or 20-22 weeks post randomisation (3 weekly group)

All groups: 4th and thereafter: 2 months after the end of trial treatment (+/- 2 weeks) and then subsequently every 4 months (+/- 2 weeks) until death or the end of the trial.

PIPAC procedure

- Participants randomised to the intervention arm will have up to 3 PIPAC procedures. PIPAC procedures can only be performed by surgeons who have completed the International Society for Study of Pleura and Peritoneum (ISSPP) PIPAC course. One of the Cis or Co-Investigator (Professor Jamie Murphy) will observe the first PIPAC case performed at each PIPAC site (excluding Imperial and Cardiff). ISSPP training courses will be held at periodic intervals likely in Cardiff.
- A minimum of 2 surgeons at any one time must be trained to ISSPP standards in PIPAC and have passed the course at any one time for the site to be able to be authorised to perform PIPAC in the trial. Other requirements for PIPAC are as follows (note that these must be available for the duration of time that the site is planning to perform PIPAC in the trial):
  - Aseptic pharmacy facilities / services
  - Laminar airflow and controlled aerosol waste disposal systems.
  - A pressuriser that meets requirements for PIPAC administration (a high pressure injector capable of remote activation and delivering 20Bar pressure at rate of 30ml/min e.g., Medtron Accutron Thera. It is hoped that most sites will already have one of these on site or can repurpose one for use in PIPAC from their radiology departments.
  - Theatres made available for PIPAC to take place along with sufficient anaesthetist, surgeon and theatre staff time.
- Sites will be provided with a PIPAC manual and training for all staff will be provided at site initiation, including guidance on general anaesthetic during the procedure, post operative management and consenting for PIPAC as part of the PICCOS trial.
- In addition to trial specific consent, patients undergoing PIPAC as part of the trial will need consenting as part of usual NHS processes prior to each PIPAC procedure.
- It is recognised that it may be challenging to ensure that theatres/staff/patients are available at the times required in the protocol and to ensure that there are no unnecessary delays in the timing

of PIPAC procedures, a PICCOS specific Research Nurse will be employed by the Sponsor organisation with the main aim of supporting the surgical logistics of the trial.

Patient payments

The trial team will reimburse patients for travel expenses for their PIPAC procedures.

Site payments

The following are classified as 'Research Costs' in the trial:

- CRF completion
- Ranodmisation
- Administer quality of life questionnaires
- 2 CT scans during the follow up period if additional to SOC
- Upload of a copy of CT imaging to Cimar platform for central review of primary endpoint
- Review and reporting of AEs / SAEs
- SIV training time
- Time for staff to attend monitoring visit
- Site archiving cost

The following are classified as 'Excess Treatment Costs' in the trial:

- Nebulusers required for PIPAC procedure (e.g. MRC-4 TOPOL delivery system) – *sites will be required to purchase these directly at a discounted price – further information will be provided in due course.*
- Surgeon, Anaestetist and theatre staff time to perform PIPAC procedure
- Equipment needed for the general anaesthetics and laparocopic surgery procedure

We are applying and aim to secure funding for the following ETCs to cover:

- Cost of pressuriser where site does not have one available for use *(It is hoped that most sites will have one already or be able to repurpose a pressuriser from their radiology departments for use in the PIPAC procedure)*

Further details on Research Costs and ETCs will be provided to sites in due course and can be discussed prior to signing of site contract.

Data management

PICCOS will use an electronic database to collect patient information, from eligibility data/ assessment results/ PIPAC procedure information, and so on.
If a patient will be undergoing PIPAC at a site different to the one that recruited them, both sites will have access to that patient's eCRFs.

Trial monitoring

The trial will be centrally monitored and queries/ data chases will be sent regularly via the online database and/or email.
In-person site monitoring visits may be triggered for reasons such as poor data submission, over/under reporting of SAEs, excessive queries being raised (and other reasons) etc and/or to offer support/training as required.

Qualitative interview sub studies

- A subset of patients from both the control and intervention arms, and a selection of healthcare professionals will be approached to take part in qualitative interviews with researchers from the University of Bristol. Site staff will be required to explain the sub study to patients and if the patient is interested, they will complete a 'Consent to Contact Form' which is then passed on to the CTR. Researchers for this sub study will then make direct contact with interested patients, consent remotely and arrange the interview(s) directly with the patient.
- The aims of this sub-study are included within the main study objectives in the exploratory section.